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EXAMINER	
NOBLE, MARCIA STEPHENS	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 08/09/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/507,268	YLA-HERTTUALA ET AL.	
	Examiner	Art Unit	
	Marcia S. Noble	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 May 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of Claims

1. Claims 1-12 were provisionally elected by telephonic election of restriction requirement and this election was affirmed in Applicant's response to Non-Final Rejection, filed 5/18/2006. Therefore, this restriction is made FINAL.

Claims 1, 2, and 6 have been amended and claims 13-19 have been cancelled in the above mention response.

Claims 1-12 are under consideration.

Specification

2. The disclosure, objected to because the instant application was not in compliance with the sequence rules and contained sequences without SEQ ID NOS, had been corrected by amendment, and therefore the objection is withdrawn.

Claim Rejections - 35 USC § 112, 1st paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 1-13 were rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the following: 1) a baculovirus comprising a vp39-green fluorescent protein fusion, wherein the fusion protein is expressed on the

surface of the baculovirus capsid; and 2) an *in vitro* method for delivering a peptide into the nucleus of a eukaryotic cell comprising contacting the cell with a baculovirus comprising a vp39-green fluorescent protein fusion does not reasonably provide enablement for the other baculoviruses and methods embraced by the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. Upon further consideration, this rejection is being withdrawn in consideration of a new scope of enablement rejection as follows.

Claims 1-12 rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for for the following: 1) a baculovirus comprising a vp39 fusion protein, wherein the C- or N- terminus of the vp39 is modified and wherein fusion protein is expressed on the surface of the baculovirus capsid; and 2) an *in.vitro* method for delivering a peptide into the nucleus of a eukaryotic cell comprising contacting the cell with a baculovirus comprising a vp39 fusion protein wherein the C- or N- terminus of the vp39 is modified and wherein fusion protein is expressed on the surface of the baculovirus capsid, does not reasonably provide enablement for 1) a buculovirus of which the capsid has been modified wherein any capsid protein or p 24 or p80 are modified such that said capsid displays one or more heterologous peptides, and 2) an *in vitro* method for delivering a peptide into the nucleus of a eukaryotic cell comprising contacting the cell with a baculovirus wherein the capsid has been modified wherein any capsid protein or p 24 or p80 are modified such that said capsid displays one or more heterologous peptides. The specification does not enable any person

skilled in the art to which it pertains, or with which it is most nearly connected, to use or make the invention commensurate in scope with these claims.

While determining whether a specification is enabling, one considers whether the claimed invention provides sufficient guidance to make or use the claimed invention, if not, whether an artisan would require undue experimentation to make and use the claimed invention and whether working examples have been provided. When determining whether a specification meets the enablement requirements, some of the factors that need to be analyzed are: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and whether the quantity of any necessary experimentation to make or use the invention based on the content of the disclosure is "undue".

Furthermore, USPTO does not have laboratory facilities to test if an invention will function as claimed when working examples are not disclosed in the specification, therefore, enablement issues are raised and discussed based on the state of knowledge pertinent to an art at the time of invention, therefore skepticism raised in the enablement rejections are those raised in the art by artisans of expertise.

The claims are directed to a baculovirus comprising a modified capsid protein, wherein the modified protein is vp39, p24 or p80. The claims are further directed to methods for delivering a peptide into the nucleus of a cell comprising contacting the cell with the same baculovirus.

The specification discusses that the invention features a baculovirus comprising a modified capsid protein. The specification discloses that both the N and C terminus of the vp29 can be modified without affecting their structural/functional roles in the baculovirs. The specification further discusses that such a baculovirus could be used for delivering a peptide to the nucleus of a cell, for therapeutic benefit or for studying nuclear transport of the baculovirus capsid. See the specification at page 4, at lines 5-12, and also at page 5, at lines 17-28. While the specification provides extensive teachings pertaining to creation of a baculovirus comprising a modified vp39 capsid protein, wherein the modified vp39 comprises a fusion of vp39 and green fluorescent protein (GFP), and wherein the fusion protein is expressed on the surface of the baculovirus capsid, the specification fails to provide any relevant teachings or specific guidance with regard to creation of the other baculoviruses that display heterologous proteins on their capsids as embraced by the claims. Also, the specification has provided guidance for in vitro methods of delivering a peptide into the nucleus of a eukaryotic cell but has failed to provide guidance or working examples correlating to in vivo delivery of a peptide into the nucleus of a eukaryotic cell. Given the lack of guidance provided by the specification it would have required undue experimentation to make and use the invention as claimed.

While the specification provides specific guidance on how to modify the vp39 without altering it structure/function relationship, it does not provide guidance on how to modify p24, p80, or make any other modifications within the vp39 other than the at the termini of the sequences that will maintain the production of a baculovirus that is

capable of delivering a peptide into the nucleus of a cell. Oke-Blom et al (Briefing in Functional Genomics and Proteomis 2(3):244-253, 2003) suggest that the three dimensional structure of baculovirus *AcMNPV* has not been determined and therefore the structural interactions and functional elements of capsid proteins have not been fully described, developed, and understood (p. 249, col 1 par 1). Since the structure/function of the capsid proteins of baculovirus have not been well described in the art, an artisan would need to look to over examples in the art to determine functional/structural limitations of capsid proteins. Thomsen et al (J Virol 69(6):3690-3703, 1995) disclose that the C-terminal 25 amino acids of the UL26 and UL26.5 capsid protein must remain unaltered to assure proper assembly of the capsid in HSV-1 (see abtract). West et al teach (J Virol 80(9):4458-4468, 2006) that the E2 domain (E2 amino acids 408 to 415 are critical for nucleocapsid formation an Sindbis virus assembly and that mutation in these residues result in failure to assemble virons (see abstract). These art suggest that there are limits to the modifications that can be made to capsid and still retain their structure functions relationship. The instant specification only teaches modification to one capsid protein, vp39 at the N- and C- terminus. The specification contemplates the modification of p24 and p80, but does not provide any guidance as to the structural/functional elements that must be conserved in p24 or p80. Therefore, an artisan would not know which amino acids of p24 or p80 or other capsid protein that could be altered and still provide a virion formation. The specification also does not provide modification other then at the N and C terminus of vp39 that do not hinder the function of vp39. Therefore, an artisan would only know how to make such a

modification to other parts of the sequence because, again the art nor the specification do not teach the region of the vp39 sequence that must be conserved for function. Furthermore, for an artisan to determine the region of vp39 or other capsid proteins necessary for function, they would have to do trial and error mutagenesis analysis that goes beyond the realms of optimization and this level of experimentation would be considered undue.

The specification has taught that baculoviruses are unpredictable with respect to transduction of mammalian cells due to a transport block between the cytosol and the nucleus. For example, see page 10 of the specification. Moreover, the state of the art as evidenced by Kukkonen et al reported that a vp39-egfp baculovirus did not enter the nucleus of human cells (EAHY, MG63 and NHO) but was able to enter the nucleus of Pk1 pig cells. See page 856, in column 2, in the discussion section. The observations of Kukkonen et al support the unpredictable nature of mammalian cell transduction by baculoviruses. Kukkonen et al went to characterize baculovirus entry and release of viral capsid into mammalian cells as general phenomena. Finally, Kukkonen et al discussed the difficulties of target cell transduction, which include internalization, escape from endosome and transport of the genetic material to the nucleus. While transduction can be improved by selection of cell membrane targeting moieties, routing from the cytosol to the nucleus remains difficult to achieve. See Kukkonen et al at page 857, in column 2. In light of the above, the specification has failed to provide guidance to overcome the unpredictability of transducing cells with a baculovirus, particularly cells *in vivo* for therapeutic benefit resulting from delivery of a peptide. Given the lack of

guidance provided by the specification it would have required undue experimentation to make and use the invention as claimed without a reasonable expectation of success.

In the Applicants response, second argument concerning delivery of a peptide to the nucleus was traversed on the grounds that Kukkonen et al demonstrates that the baculovirus capsid is transported to the nucleus. However, this again was not a the case for all cell types or capsid proteins. Vp39 modification was not able to enter the nucleus of several human cell types suggestive of a cell specificity and unpredictability in the ability to related this concept to all cell types that can be transfected by baculovirus with the any modification to capsid proteins.

Overall, the rudimentary sate of the art and the lack of specific guidance as to modification to capsid proteins of baculovirus that will still enable for function and deliver a peptide to the nucleic of a transfected cell fails to enable an artisan to use or make the instant invention in its full scope and only enables the use and make of a baculovirus with a modification to the N or C terminus of the vp39 capsid protein.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

4. Claims 1-7 and 10-11 stand rejected under 35 U.S.C. 102(b) as being anticipated by Liu et al (Acta Virolgica, 2000, 44: 157-161).

The rejection was based on the interpretation that "modified" could refer to a natural modification that evolves between different strains and the express a heterologous protein I its capsid" is suggestive of intent and not give patentable weight, and therefore Liu et al anticipated the instant invention.

Applicant traversed this rejection on the grounds that Liu et al does not teach a heterologous protein and that the amended claims correct the issue of intent by specifying the heterologous protein is displayed on the capsid.

These arguments are not found persuasive because of the breadth of "heterologous". As Applicant teaches in their response, heterologous is not present in the naturally occurring capsid or in other words would be an exogenous sequence to the capsid. However, a heterologous peptide would include the scenario of adding a region of an exogenous capsid gene that has 100% homology with a peptide sequence of the endogenous capsid gene by recombination. Given that the claims do not disclose the extent of modification to the capsid (where in the capsid protein sequence and how), the instant claims would read on an exogenous sequence that is 100% homologous endogenous sequence, because a there would be no identifiable structural difference between the modified capsid expressing the heterologous peptide with 100% homology and the naturally occurring capsid peptide. Therefore, both the Chinese and Japanese isolated of bombyx mori nucleopolyhedrovirus would anticipate the instant inventions. Therefore, the instant rejection stands.

5. Claims 10 and 12 stand rejected under 35 U.S.C. 102(b) as being anticipated by Van Loo et al (Journal of Virology, 2001, 75(2): 961-970; IDS). The rejection of claims 6-9 for being anticipated by Van Loo et al is withdrawn because amendment of claim 6 overcomes the rejection.

The instant claims were rejected on the grounds that baculovirus expressing humanized GPF would anticipate the claims because the phrases, "the capsid has been modified to display one or more heterologous peptides" and "to express one or more heterologous peptides in its capsid", are intentional language not functional language and therefore have no patentable weight. Claims 10 and therefore dependent claim 12, were not amended an still contain the intentional language. Therefore, the rejection stands.

However, claim 6 and therefore dependent claims 7-9 have been amended to incorporate functional language that specifies that the heterologous be expressed and displayed on the capsid. The GFP of the disclosed baculovirus is not specifically expressed and displayed in the capsid; therefore, no longer anticipate these claims. Therefore the rejection of claims 6-7 is withdrawn. However, the rejection of claims 10 and 12 stand.

6. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Marcia S. Noble whose telephone number is (571) 272-5545. The examiner can normally be reached on M-F 9 to 5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Marcia S. Noble